2. RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS

Claims 1-21, 23-33, 35, 36, and 44-51 were pending at the time of the Action.

Claims 8, 21, 45, and 49 have been canceled herein without prejudice or disclaimer.

Claims 1, 9-11, 13-16, 23-24, 26, 29, 44, 46, 48, and 50 have been amended herein.

Claims 1-7, 9-21, 23-33, 35, 36, 44, 46-48, and 50-51 remain pending in the application.

2.2 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original claims, specification and figures as filed.

Specific support for amended claims 1, 14, 15, 16, and 29 can be found at least on page 14, lines 9 and 18 of the originally published PCT application.

Additional support for amended claims 1, 14, 15, 16, 29, and specific support for amended claims 44 and 48 can be found at least on page 30, line 5 of the originally published PCT application.

It is Applicants' belief that no new matter is included as a result of the accompanying amendment.

2.3 THE REJECTIONS UNDER 35 U.S.C. § 112, 1ST PARAGRAPH, HAVE BEEN OVERCOME.

Claims 1-21, 23-33, 35-36 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Action objected to the limitation "other than an adult in congestive heart failure" recited in the rejected claims as being "new matter". On pages 2 and 3 of the Action, the Office alleges that the specification does not "provide explicit or implicit indication to one of skill in the art that possible exclusion of this group of patients was originally contemplated as part of applicant's invention, and such possibility does not satisfy the written description requirements of 35 USC 112, first paragraph."

Applicants respectfully traverse, and call the Examiner's attention to page 14 of the specification, line 9 where the inventors note that the non-skeletal contribution of circulating NT-CNP levels in the growing period is "likely to be small since (i) NT-CNP concentrations are not affected by heart disease (unless very severe), and are minimally affected by severe endothelial disease."

Thus, it is clear that Applicants original specification contemplated, enabled, *and* provided necessary written description for limiting the claimed methods to patients other than those adults having a severe heart disease, such as, for example, congestive heart failure.

However, to fully comply with the Office's request for clarity of the rejected claims, Applicants have amended the claim language to more broadly recite the generic condition of "severe heart disease" for which exact, literal written description, exists in the specification as originally filed. Applicants believe this amendment fully addresses the Examiner's concerns, and as such, respectfully requests that the rejection now be withdrawn.

Claims 1-21, 23-28 and 44-51 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims.

The Action alleges on page 3 that the specification "while describing and enabling for determination of skeletal development in pre-adults, and in those suspected of having a skeletal disease or disorder, with determinations of the N-terminal fragment of pro-C-type natriuretic peptide (NT-proCNP) levels in plasma compared to levels in one or more control populations matched, for example, in age and sex, does not reasonably provide description or enablement for determinations indicative of skeletal disease or disorder in subjects with differences from a control population level generally."

Applicants respectfully traverse; however, to more distinctly point out and particularly claim the relevant subject matter, Applicants have amended the claim language to note that the test and control populations are matched with respect to age and sex. Applicants believe this amendment fully addresses the Examiner's concerns, and as such, respectfully request that the rejection now be withdrawn.

Claims 1-7, 14-20, 28-32, 36, 44, and 48 were rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification, while being enabling for methods of detecting NT-CNP levels using antibodies in immunoassays, does not provide written description or enablement for a method of measuring NT-CNP or binding agents therefor generally. The Action contends that the specification is enabling only when the method employs immunoassay detection of the target peptide.

Applicants respectfully traverse. However, without acquiescing in any way with the propriety or substance of the objection, and solely in the interest of advancing claims of particular commercial relevance to expeditious allowance, Applicants have amended the independent claims responsive to this request to insert the clarifying language as recommended by the Office.

Applicants believe this amendment fully addresses the Examiner's concerns regarding the pending claim language, and as such, respectfully request that this rejection now be withdrawn.

2.4 THE REJECTION UNDER 35 U. S. C. § 112, 2ND PARAGRAPH, HAS BEEN OVERCOME.

Claims 15 and 29-32 were rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 15 the Office considers that the relationship between elements is not sufficiently clear.

Applicants respectfully traverse; however, to more distinctly point out and particularly claim the relevant subject matter, Applicants have amended the claim language to note that the test and control populations are matched with respect to age and sex. Applicants believe this amendment fully addresses the Examiner's concerns, and as such, respectfully request that the rejection now be withdrawn.

Claim 29 was rejected allegedly as lacking sufficient antecedent basis.

Again, Applicants respectfully traverse. However, to more distinctly point out and particularly claim the relevant subject matter, Applicants have amended claim 29 to recite "comparing the levels of NT-CNP in said first and said second biological fluids, wherein a significant difference in the levels of NT-CNP in said second biological fluid compared to the level of NT-CNP in said first biological fluid indicates a change in skeletal growth rate in said subject, wherein said measuring step comprises detecting binding between NT-CNP and an antibody that selectively binds NT-CNP."

Applicants believe that this clarification completely addresses the Examiner's concern, and as such, respectfully request that the rejection be withdrawn.

2.5 THE REJECTION OF CLAIMS UNDER 35 U.S.C. § 102(B) IS OVERCOME.

Claims 1, 2, 6-9, 11-17, 21, 24-28, 33 and 36 were rejected under 35 U.S.C. § 102(b), as being anticipated by Prickett* et al. *(Biochem. Biophys. Res. Comm., 286(3):513-517, August 24, 2001; hereinafter "Prickett") for reasons similar to those of record.

Again, Applicants maintain their previous traversal of this rejection.

Applicant reminds the Office that a proper rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461 (PTO Bd. App. 1990). As stated in the decision of *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990): "(f)or a prior art reference to anticipate in terms of 35 U. S. C. § 102, every element of the claimed invention must be *identically shown in a single reference*" (Emphasis added).

Because Prickett fails to disclose each and every element of the claimed invention, Prickett *cannot* anticipate the claimed invention within the meaning of 35 U. S. C. § 102, and thus the present rejection is improper, and must be withdrawn.

Prickett describes measuring NT=CNP levels in 22 adult test subjects (ages 33-81 years, 12 males and 10 females), and in 16 adult control subjects (ages 22-55 years, 12 males and 4 females). Prickett notes that the increase in the measurement of NT-CNP levels in patients with cardiac failure was similar across different ages in both males and females, such that it was not critical in the teachings of Prickett that there was a need for age- and sex-matched controls. In Prickett, a bare, control unmatched NT-CNP level was shown to be an indication of heart disease, but no correlation between NT-CNP level and skeletal growth and development.

Therefore, the claimed invention is novel over the cited reference. As such, Applicants respectfully request that the rejection be withdrawn.

2.6 THE REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(A) IS OVERCOME.

Claims 1, 2, 6-17, 21, 23-28, 33, 35, and 36 were rejected under 35 U.S.C. § 103(a), as being legally obvious over Prickett in view of Buechler* et al. *(U.S. 2003/0219734; hereinafter "Buechler") for reasons similar to those of record.

The Action at page 8 considers that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted monoclonal antibodies and alternative assay formats such as sandwich immunoassays, as taught in Beuchler, for the polyclonal antibodies and competitive assay in Prickett et al. because to do so is notoriously old and well known in the art."

Again, Applicants respectfully maintain their previous traversal of this rejection and in doing so, notes and specifically incorporates all previous arguments to date, and particularly the remarks and arguments presented in the paper submitted in response to the previous Action.

As Applicants have noted above, Prickett describes measuring NT=CNP levels in test and control adult subjects unmatched for either age or sex. Prickett taught that an increased level of NT-CNP in patients was indicative of cardiac failure, and the results demonstrated were similar across different ages, and was observed in both males and females. There is no teaching in Prickett, either alone, or in combination with Buechler, that elevated NT-CNP levels could be correlative in skeletal growth or development.

At best, combining the teachings of Prickett and Buechler would suggest the use of a monoclonal antibody or a polyclonal antibody "cocktail" specific for NT-CNP and/or the BNP, ANP, CNP degradation fragments thereof, to determine the presence of one or more such

peptides in a sample to diagnose *congestive heart failure* in an adult subject. However, the combination would certainly not teach or suggest that correlating the amount of NT-CNP in age- and sex-match pre-adults would provide a prognostic of skeletal growth or development in such pre-adult subjects.

From Prickett and Buechler, the mere presence of one or more fragments in the adult patient sample was considered indicative of heart disease. The actual level need not even be determined (see Buechler paragraph [0047]), and thus, would not have required careful comparison with an age- and sex-matched control. This is also evidenced by paragraphs [0086-0088] of Buechler which states simply that the same number of "disease" patients and "non-disease" patients were assigned to each group to assess which of the ANP/BNP/CNP degradation fragments were useful as markers of congestive heart disease.

There is certainly no suggestion or motivation in either of the cited references to measure NT-CNP levels in patients and in age- and sex-matched controls to assess skeletal growth and/or development in the patient. Applicants assert, therefore, that the amended claims are non-obvious in view of the combination of Prickett and Buechler, and as such, respectfully request that the rejection be withdrawn.

2.7 CONCLUSION

It is respectfully submitted that all claims are fully-enabled by the Specification, that all pending claims are definite, and that the inventions embodied in those claims are useful, novel, and non-obvious. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance. Applicants earnestly solicit concurrence

by the Examiner and the issuance of a Notice of Allowance in the case with all due speed. Applicants note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

July 20, 2009
Date

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